Complete Summary

GUIDELINE TITLE

United Kingdom national guideline on the management of the viral hepatitides A, B, and C 2005.

BIBLIOGRAPHIC SOURCE(S)

United Kingdom national guideline on the management of the viral hepatitides A, B & C. London (England): British Association for Sexual Health and HIV (BASHH); 2005. 22 p. [191 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline on the management of the viral hepatitides A, B, and C. London (England): Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 16, 2007, Baraclude (Entecavir): Revisions to the prescribing information for Baraclude to indicate that the drug is not recommended for HIV/hepatitis B virus (HBV) co-infected patients who are not also receiving highly active antiretroviral therapy (HAART) due to the potential for the development of HIV resistance.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Viral hepatitides A, B, and C (hepatitis A, hepatitis B, hepatitis C)

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Treatment

CLINICAL SPECIALTY

Infectious Diseases
Obstetrics and Gynecology
Urology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To present a national guideline on the management of viral hepatitides A, B, and C
- To offer recommendations on the diagnostic tests, treatment regimen, and health promotion principle needed for the effective management of hepatitis A, B, and C

TARGET POPULATION

Patients (primarily those aged 16 and older) in the United Kingdom with:

- Hepatitis A
- Hepatitis B
- Hepatitis C

INTERVENTIONS AND PRACTICES CONSIDERED

Assessment/Diagnosis

Viral Hepatitis A

1. Assessment of clinical features
2. Serology: serum hepatitis A virus specific immunoglobulin M (IgM)
3. Other diagnostic tests
    - Serum/plasma aminotransferases
    - Bilirubin
    - Alkaline phosphatase levels
    - Prothrombin time

Viral Hepatitis B

1. Assessment of clinical features
2. Hepatitis B serology
    - Surface antigen (HBsAg)
    - "e" antigen (HBeAg)
    - Immunoglobulin M (IgM) anti-core antibody
    - Immunoglobulin G (IgG) anti-core antibody
    - Hepatitis B virus deoxyribonucleic acid (DNA)
    - Antibody to hepatitis B e antigen (anti-HBe)
    - Antibody to hepatitis B surface antigen (anti-HBs)
    - Antibody to hepatitis B core antigen (anti-HBc)
3. Other diagnostic tests
    - Serum/plasma aminotransferases
    - Bilirubin
    - Alkaline phosphates levels
    - Prothrombin time

Viral Hepatitis C

1. Assessment of clinical features
2. Serology
    - A screening antibody test: enzyme-linked immunoassay, recombinant immunoblot assay
    - Molecular biological techniques such as a reverse transcription-polymerase chain reaction (RT-PCR) assay for viral ribonucleic acid (RNA)
3. Other diagnostic tests
    - Acute infection, as for hepatitis A
    - Chronic infection, as for hepatitis B

Management/Treatment

Viral Hepatitis A

1. General advice and patient education
2. Screening for other sexually transmitted infections in cases of sexually acquired hepatitis
3. Criteria for inpatient or outpatient treatment in acute icteric hepatitis
4. Considerations for pregnant and breastfeeding women
5. Management of sexual contacts and other contacts
    - Partner notification
    - Human normal immunoglobulin
    - Hepatitis A vaccine

6. Follow-up
7. Primary prevention: vaccination recommendations and education

Viral Hepatitis B

1. General advice and patient education
2. Screening for other sexually transmitted diseases in cases thought to have been sexually acquired or otherwise appropriate
3. Liver biopsy for assessment of chronic disease
4. Criteria for inpatient or outpatient treatment in acute icteric hepatitis (same as hepatitis A)
5. Pharmacotherapy for chronic infection (lamivudine, adefovir, alpha interferon, pegylated interferons, entecavir, emtricitabine, tenofovir)
6. Considerations for pregnant and breastfeeding women
7. Management of sexual contacts and other contacts
    - Partner notification, contact tracing, screening, and education
    - Hepatitis B immunoglobulin
    - Accelerated course of recombinant vaccine
8. Follow-up
9. Screening and primary prevention activities, such as vaccination

Viral Hepatitis C

1. General advice and patient education
2. Pharmacotherapy: alpha interferon, ribavirin, pegylated alpha interferon
3. Vaccination against hepatitis A and B
4. Considerations for pregnant and breastfeeding women
5. Management of sexual contacts and other contacts: partner notification and contact tracing
6. Follow-up
7. Screening and primary prevention
    - Testing for hepatitis C
    - Needle and syringe exchange schemes

MAJOR OUTCOMES CONSIDERED

- Rates of infection of viral hepatitis A, B, and C
- Morbidity and mortality due to viral hepatitis A, B, or C infection and complications of infection

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Search Strategy

For each type of hepatitis, a Medline search was performed for the years 1966 to 2004 (Feb.) for hepatitis types A and B and 1990 to 2004 (Feb) for hepatitis C. From the Medical Subject Heading (MeSH) terms "hepatitis A," "hepatitis B," and "hepatitis C," the following sub-headings were used: Complications, Drug Therapy, Diagnosis, Epidemiology, Etiology, Mortality, Prevention and Control, Therapy, Transmission, Virology. The searches were limited to "human" for all searches. For Drug Therapy, Prevention & Control, and Therapy, searches were limited initially to "randomized controlled trials" but in the absence of enough publications this was changed to "controlled clinical trials," "clinical trials," or "reviews" in that order. For the sub-headings other than these three the search was limited to "reviews." Textword searches for "hepatitis A," hepatitis B," and "hepatitis C" were combined, as appropriate, with textword searches for " complication$," "diagnosis," "prevention," "transmission," "immunoglobulin," "vaccine," "non-response," "non-responders," "HIV," "randomized controlled trial," "lamivudine," "famciclovir," "ribavirin."

Criteria for inclusion:

- Evidence from randomised controlled trials (RCTs) was used where possible, and failing that the studies using other rigorous scientific method.
- Recommendations were based on RCT or other scientific evidence and graded accordingly.
- No harms are anticipated.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence:

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grading of Recommendations:

A (Evidence Levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation

B (Evidence Levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation

C (Evidence Level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities
- Indicates absence of directly applicable studies of good quality

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Prior to publication the final draft of the guideline was placed on the British Association for Sexual Health and HIV (BASHH) Web site, and copies circulated to the BASHH branch chairs, Genito-Urinary Nurses Association (GUNA), and Scottish Health Advisory Service (SHAS) chairs for comment and peer review. After a period of three months any comments received were reviewed by the guideline authors and acted on appropriately before final authorisation by the Clinical Effectiveness Group (CEG) was given and publication was undertaken.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (I-IV) and grades of recommendation (A-C) are repeated at the end of the "Major Recommendations" field.

Hepatitis A Virus Infection

Diagnosis

Serology

- Confirmed by a positive serum hepatitis A virus-specific immunoglobulin M (HAV-IgM) which remains positive for 6 months or more (Kotwal, 2000; Liaw et al., 1986). Hepatitis A virus-immunoglobulin G (HAV-IgG) does not distinguish between current or past infection and may remain positive for life (Kotwal, 2000; Stapleton, 1995).

Other Tests

Serum/plasma aminotransferases (AST/ALT) 500 to 10,000 IU/L. Bilirubin up to 500 micromoles/L. Alkaline phosphatase levels <2x the upper limit of normal, but higher if there is cholestasis (McIntyre, 1990; Bianco et al., 2003; Willner et al., 1998; Pramoolsinsap, 2000).

Prothrombin time (PT) prolongation by more than 5 seconds suggests developing hepatic decompensation (McIntyre, 1990; Bianco et al., 2003).

Management

General Advice

- Patients should be advised to avoid food handling and unprotected sexual intercourse until they have become non-infectious (Level of evidence III,

Grade of recommendation B) (Maguire et al., 1995; Shapiro & Margolis, 1993; Minuk et al., 1994; Massoudi et al., 1999; Oxman et al., 1994).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Hepatitis A is a notifiable disease.

Further Investigation

Screen for other sexually transmitted infections in cases of sexually-acquired hepatitis or if otherwise appropriate.

Acute Icteric Hepatitis

- Mild/moderate (80%), manage as an outpatient emphasising rest and oral hydration (Level of evidence III, Grade B recommendation) (McIntyre, 1990).
- Severe attack with vomiting, dehydration, or signs of hepatic decompensation (change in conscious level or personality), admit to hospital (Level of evidence III, Grade B recommendation) (Bianco et al., 2003; Willner et al., 1998).

Pregnancy and Breast Feeding

- Pregnant women should be advised of the increased risk of miscarriage/premature labour and the need to seek medical advice if this happens (Medhat et al., 1993).
- Breast-feeding can be continued but consider giving human normal immunoglobulin (HNIG) 125 mg intramuscularly (i.m.) to the baby, although most children will have mild or asymptomatic infection (Level of evidence IV, Grade C recommendation) ("Hepatitis A," 1996).

Sexual and Other Contacts

- Partner notification should be performed for at-risk homosexual contacts (oro/anal, digital/rectal, and penetrative anal sex) within the period 2 weeks before to 1 week after the onset of jaundice. This to be documented and the outcome documented at subsequent follow-up. Other people thought to be at risk (household contacts, those at risk from food/water contamination) to be contacted via the public health authorities (consultant in communicable disease control [CCDC] or equivalent). The CCDC has a duty of confidentiality to the index patient.
- Hepatitis A vaccine may be given up to 7 days after exposure providing exposure was within the infectious period of the source case (during the prodromal illness or first week of jaundice) (Level of evidence IIa, Grade B recommendation) ("Hepatitis A," 1996; Crowcroft et al., 2001; Irwin & Millership, 1999; Mele, 1999).
- HNIG, 250 to 500 mg intramuscularly, should be considered for patients at higher risk of complication (concurrent chronic hepatitis B or C, chronic liver disease, or age >50 yr) or if there has been a delay of more than 7 days after exposure (Level of evidence Ib, Grade A recommendation) ("Hepatitis A," 1996; Crowcroft et al., 2001).

- HNIG works best if given in the first few days after first contact, with an efficacy of 90%, and is unlikely to give any protection more than 2 weeks after first exposure, but may reduce disease severity if given up to 28 days after exposure (Crowcroft et al., 2001).
- Patients are most infectious for 2 weeks before the jaundice (i.e., before the illness is recognised).
- Hepatitis A vaccine schedule: doses at 0 and 6 to 12 months, 95% protection for at least 5 years (Level of evidence Ib, Grade A recommendation) ("Prevention of hepatitis A," 1999; Van Damme et al., 2003; Chan et al., 1999; Kemper et al, 2003). Current advice is to revaccinate after 10 years (Level of evidence IIb, Grade B recommendation) ("Prevention of hepatitis A," 1999; Van Damme et al., 2003; Chan et al., 1999; Kemper et al, 2003; Neilsen, Bodsworth, & Watts, 1997); however there is increasing evidence that vaccine-induced immunity may be >20 years and possibly lifelong, so no further booster doses may be needed after the primary course in immunocompetent patients ("Prevention of hepatitis A," 1999; Van Damme et al., 2003).
- Human immunodeficiency virus (HIV)-positive patients respond (antibody production) in 73 to 88%, but titres are lower than in HIV-negative individuals (Level of evidence IIa, Grade B recommendation) (Kemper et al., 2003; Neilson, Bodsworth, & Watts, 1997). If patients with a low CD4 count (<300 cells/mm^3) are vaccinated, they should be revaccinated if the CD4 count rises above 500/mm^3 as a result of highly active antiretroviral therapy (HAART) (Neilson, Bodsworth, & Watts, 1997; Nelson et al., 2003).
- There is a combined hepatitis A+B vaccine given on the same schedule as the hepatitis B vaccine and has similar efficacy to the individual vaccines although early immunity to hepatitis B may be impaired (Level of evidence IIa, Grade B recommendation) (Thompson & Norris, 1998; Frey et al., 1999).
- If an outbreak is suspected or if the index case is a food handler, notify the local CCDC/public health department by telephone (Level of evidence IV, Grade C recommendation) ("Hepatitis A," 1996; Crowcroft et al., 2001).

Follow-up

- See at 1 or 2 weekly intervals until aminotransferase levels are normal (usually 4-12 weeks) (Level of evidence IV, Grade C recommendation).
- Immunity is lifelong (Kotwal, 2000; Stapleton, 1995).

Primary Prevention

- Current evidence still suggests that most men who have sex with men are not at increased risk for hepatitis A infection (Villano et al., 1997; Ross et al., 2002; Corona et al., 1999) and therefore universal vaccination in this group cannot be firmly recommended (Level of evidence III, Grade B recommendation). However, many outbreaks have been reported amongst homosexual men in large cities and therefore clinics in these areas (e.g., central London) should offer vaccination, particularly when increased rates of infection in gay men have been recognised locally (Level of evidence III, Grade B recommendation) (Stewart & Crofts, 1993; Leentvaar-Kuijpers et al., 1995; Cotter et al., 2003; Bell et al., 2001; Villano et al., 1997; Reintjes et al., 1999; Ferson, Young, & Stokes, 1998; "Hepatitis A," 1996; Crowcroft et al., 2001).

- Intravenous drug users and patients with chronic hepatitis C infection should also be vaccinated (Level of evidence III, Grade B recommendation) (Ida et al., 2002; Sundkvist et al., 2003; Perrett et al., 2003; Pramoolsinsap, 2000; "Hepatitis A," 1996; Crowcroft et al., 2001).
- Vaccination is also recommended for travellers to developing countries, people with haemophilia or chronic liver disease, those with occupational exposure, and for people at risk in an outbreak (Level of evidence Ib, Grade A recommendation) ("Hepatitis A," 2004; "Hepatitis A," 1996; Crowcroft et al., 2001).
- Health/sex education should stress the routes of transmission and the higher incidence in developing countries (Level of evidence IV, Grade C recommendation) ("Hepatitis A," 1996).

Hepatitis B Virus Infection

Diagnosis

See Table

Table. Hepatitis B Serology (Kotwal, 2000; Hoofnagle, 1990; Gitlin, 1997)

Stage of infection	Surface antigen (HBsAg)	"e" antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs
Acute (early)	+	+	+*	+	+	-	-
Acute (resolving)	+	-	+	+	-	+/-	-
Chronic (high activity)	+	+/-	-	+	+	+/-	-
Chronic (low activity)	+	-	-	+	-	+/-	-
Resolved (immune)	-	-	-	+	-	+/-	+/-
Successful vaccination	-	-	-	-	-	-	+

* In very early infection the IgM anti-core can be negative and by definition so can the IgG.

Other Tests

- Acute infection: see hepatitis A.
- Chronic infection: in most cases the only abnormality to be found will be mildly abnormal aminotransferase levels (usually <100 IU/L) and in many the liver function tests will be normal. Only in severe late stage liver disease do the liver function tests become grossly abnormal (Hoofnagle, 1990; Gitlin, 1997; Brook et al., "Randomised controlled trial of lymphoblastoid," 1989;

Brook et al., "Randomised controlled trial of interferon," 1989; Brook, Karayiannis, & Thomas, 1989). Disease activity correlates with HBV-DNA levels and $>10^5$copies/ml is regarded as significant and meriting consideration of therapy.

Management

General Advice

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact, until they have become non-infectious or their partners have been successfully vaccinated (see below) (Level of evidence III, Grade B recommendation) (Davis, Weber, & Lemon, 1989; Hoofnagle, 1990; Struve et al., 1990; "Hepatitis B," 1996; el-Dalil et al., 1995).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s) and routes of transmission of infection (see below) and advised not to donate blood (Level of evidence IV, Grade C recommendation) ("Hepatitis B," 1996).
- Hepatitis B is a notifiable disease.

Further Investigations

- Screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (Level of evidence IIb, Grade B recommendation) (Health Protection Agency, 2004; Hyams, Phillips, & Tejada, 1990).
- Other tests such as liver biopsy (for assessment of chronic disease) should be performed only by specialists in this field (Level of evidence IV, Grade C recommendation) (Hoofnagle, 1990; Gitlin, 1997; Brook et al., "Randomised controlled trial of lymphoblastoid," 1989; Brook et al., "Randomised controlled trial of interferon," 1989; Brook, Karayiannis, & Thomas, 1989).

Acute Icteric Hepatitis

As for hepatitis A.

Treatment of Chronic Infection

- Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of liver disease (Level of evidence IV, Grade C recommendation).
- Patients should be considered for therapy with lamivudine, adefovir, or alpha interferon (Level of evidence Ib, Grade A recommendation) (Brook et al., "Randomised controlled trial of lymphoblastoid," 1989; Brook et al., "Randomised controlled trial of interferon," 1989; Brook, Karayiannis, & Thomas, 1989; Chien et al., 2003; Janssen et al., 1999; Carreno et al., 1999; Lai et al., 1997; Peters et al., 2004). Additional promising treatments include pegylated interferons (Level of evidence III, Grade C recommendation), entecavir (Level of evidence III, Grade C recommendation), and emtricitabine

(FTC) (Level of evidence III, Grade C recommendation) (Craxi & Cooksley, 2003; Honkoop & De Man, 2003; Gish et al., 2002). Treatment responders have long-term benefits in terms of reduced liver damage and decreased risk of liver cancer (Janssen et al., 1999; Carreno et al., 1999; Lai et al., 1997; Peters et al., 2004; Ryu et al., 2003; Marcellin et al., 2003; Craxi & Cooksley, 2003; Honkoop & De-Man, 2003; Gish et al., 2002; Ikeda et al., 1998; Lin et al, 1999).

- Lamivudine, adevofir, and tenovir will suppress hepatitis B viral replication during therapy of immunocompromised patients, including those with HIV (Brook, Gilson & Wilkins, 2003; Dore et al., 1999; Benhamou, Bochet, & Thibault, 2001; Nelson, Portsmouth & Stebbing, 2003), and may delay liver damage (Level of evidence IIb, Grade B recommendation) (Dore et al., 1999; Benhamou, Bochet & Thibault, 2001; Nelson, Portsmouth, & Stebbing, 2003). Cure is unusual in these patients, anti-viral resistance often develops after prolonged monotherapy, and rebound hepatitis can occur if the agent is stopped or if resistance ensues (Level of evidence IIb) (Dore et al., 1999; Benhamou, Bochet, & Thibault, 2001; Nelson, Portsmouth, & Stebbing, 2003).
- Specific therapy is otherwise not indicated unless decompensated liver disease ensues (Level of evidence IV, Grade C recommendation) (Hoofnagle, 1990).

Pregnancy and Breast Feeding

- Vertical transmission (mother to infant) of infection occurs in 90% of pregnancies where the mother is hepatitis B e antigen positive and in about 10% of surface antigen positive, e antigen negative mothers. Most (>90%) of infected infants become chronic carriers (Brook et al., "Antenatal screening," 1989; Kiire, 1996; Andre & Zuckerman, 1994).
- Infants born to infectious mothers are vaccinated from birth, usually in combination with hepatitis B specific immunoglobulin, 200 IU intramuscularly (Level of evidence Ia, Grade A recommendation) (Brook et al., "Antenatal screening," 1989; Andre & Zuckerman, 1994; Michielsen & Van Damme, 1999). This reduces vertical transmission by 90%.
- There is some evidence that treating the mother in the last month of pregnancy with lamivudine may further reduce the transmission rate if she is highly infectious (HBV-DNA $\geq 1.2 \times 10^9$ geq/mL) (Level of evidence III, Grade C recommendation), but this needs to be further substantiated (van-Zonneveld, et al., 2003).
- Infected mothers should continue to breast feed as there is no additional risk of transmission (Level of evidence II, Grade B recommendation) (Hill, Sheffield, & Kim, 2002).

Sexual and Other Contacts

Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (Level of evidence IV, Grade C recommendation) (Oxman et al., 1994). The infectious period is from 2 weeks before the onset of jaundice until the patient becomes surface antigen negative. In cases of chronic infection, trace contacts as

far back as any episode of jaundice or to the time when the infection is thought to have been acquired, although this may be impractical for periods of longer than 2 or 3 years. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth (Level of evidence IV, Grade C recommendation) ("Hepatitis B," 1996). For screening of other non-sexual partners who may be at risk, discuss with the CCDC or equivalent.

Specific hepatitis B immunoglobulin 500 IU intramuscularly (HBIG) may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure/needlestick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than 7 days (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; "Editorial: Specific immunoglobulin," 1975).

An accelerated course of recombinant vaccine should be offered to those given HBIG plus all sexual and household contacts (at 0, 7, and 21 days or 0, 1, 2 months with a booster at 12 months in either course) (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; Palmovic et al., 1993;van Zonnefeld et al., 2003; Hill, Sheffield, & Kim, 2002; Francis et al., 1982; Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell & Tompkins, 2002). Vaccination theoretically will provide some protection from disease when started up to six weeks after exposure.

Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10 IU/L) (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; van Zonnefeld et al., 2003; Hill, Sheffield, & Kim, 2002; Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002).

The ultra-rapid vaccination schedule (0, 7, 21 days) leads to an anti-HBs antibody response in only 80% of recipients 4-12 weeks after the third dose (Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002). This rises to 95% just prior to the 12 month booster dose. It would be prudent to offer booster vaccinations of up to three further doses to the 20% of sexual or household contacts without detectable antibodies 4-12 weeks after the primary course (Level of evidence IV, Grade C recommendation), even though most would have eventually developed an antibody response.

Follow-up

- Acute infection: as for hepatitis A. In view of the possibility of chronic infection, serology should be repeated after 6 months even if the liver function tests are normal (Hoofnagle, 1990; Hyams, 1995; Gitlin, 1997).
- Chronic infection (HBeAg+ve or HBV-DNA $>10^5$IU/mL): if untreated, patients should be reviewed regularly at intervals of 1 year or less, ideally by a physician with expertise in this disease (Level of evidence IV, Grade C recommendation) (Hoofnagle, 1990; Hyams, 1995).
- Immunity after recovery from infection (surface antigen negative) is lifelong in over 90%.

Screening and Primary Prevention

- Hepatitis B testing in asymptomatic patients should be considered in men who have sex with men, sex workers (of either sex), intravenous drug users, HIV-positive patients, sexual assault victims, people from countries where hepatitis B is common (outside of Western Europe, North America, and Australasia), needle-stick victims, and sexual partners of positive or high-risk patients (Level of evidence IV, Grade C recommendation) (Ward, Day, & Weber, 1999; "Hepatitis B," 1996; el-Dalil et al., 1995; van Zonnefeld et al., 2003; Hill, Sheffield, & Kim, 2002). If non-immune, consider vaccination (see below) (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; Palmovic et al.; Francis et al., 1982; Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002). If found to be chronic carriers consider referral for therapy (Level of evidence Ia, Grade A recommendation) (Brook et al., "Randomised controlled trial of lymphoblastoid," 1989; Brook et al., "Randomised controlled trial of interferon," 1989; Brook, Karayiannis, & Thomas, 1989; Chien et al., 2003; Janssen et al., 1999; Carreno et al., 1999; Lai et al., 1997; Peters et al., 2004; Ryu et al., 2003; Marcellin et al., 2003; Craxi & Coosley, 2003; Honkoop & De-Man, 2003; Gish et al., 2002; Ikeda et al., 1998; Lin et al, 1999).
- The simplest initial screening test in someone who is unvaccinated or is of unknown infection status is anti-hepatitis B core antigen (anti-HBc), with the addition of other tests as necessary (Level of evidence III, Grade B recommendation) (Allain et al., 1999; Kotwal, 2000). Some also screen for hepatitis B surface antigen (HBsAg) initially (Level of evidence IV, Grade C recommendation) (el-Dalil et al., 1995; Lamden et al., 1998). Measure anti-HBs in those who have been vaccinated (Level of evidence Ib, Grade A recommendation) (Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002; Allain et al., 1999; Kotwal, 2000; Wong et al., 1996; Tayal & Sankar, 1994; Rey et al., 2000; Foneseca et al., 2005; Clemens et al., 1997; Goldwater, 1997; Haubitz et al., 1996; Zuckerman et al., 1997; Heineman et al., 1999; Shapira et al., 2001)
- Vaccination should be offered to non-immune patients in most of the above groups (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; Palmovic et al., 1993; Francis et al., 1982; Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002). The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic carriage (Level of evidence IV, Grade C recommendation) (el-Dalil et al., 1995).
- HIV-positive patients show a reduced response rate to the vaccine (approximately 40%) and become anti-HBs negative more quickly, although double dose vaccine increases the response by 13% (Level of evidence IIb, Grade B recommendation) (Wong et al., 1996; Tayal & Sankar, 1994; Rey et al., 2000; Fonseca et al., 2005). Offer a repeat course of three doses of vaccine, which may be double dose, for HIV-positive vaccine non-responders (Level of evidence IIb, Grade B recommendation).
- The vaccination schedules for both the monovalent and the combined hepatitis A+B vaccines are given below. The ultra-rapid 0, 7, 21 day regimen offers the advantage of potentially higher uptake of the full course. Test for response (anti-HBs >10 IU/L, ideally >100 IU/L) 4 to 12 weeks after the last dose (Level of evidence Ib, Grade A recommendation) ("Hepatitis B," 1996; Palmovic et al., 1993; Francis et al., 1982; Nothdurft et al., 2002; Saltoglu et

al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002). Only 80% of ultra-rapid vaccinees will have detectable anti-HBs antibodies at this stage (see '"Sexual and other contacts" above). If someone is at high risk of acquiring infection and is in the 20% without an early antibody response, consider further booster doses (Level of evidence IV, Grade C recommendation). They usually respond to further doses (up to three injections), ideally as a repeat course (Level of evidence Ib, Grade A recommendation) with response rates up to 100% (Level of evidence Ib, Grade A recommendation) (Clemens et al, 1997; Goldwater, 1997). Alternatively, for those at lower risk, offer a booster at 12 months by which time 95% would be anti-HBs-positive (Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002).

- New pre-S-containing vaccines (currently unlicensed) are effective (Level of evidence Ib, Grade A recommendation) and may also be used for conventional-vaccine non-responders (Level of evidence IIa, Grade B recommendation)(Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002; Allain et al., 1999; Kotwal, 2000; Wong et al., 1996; Tayal & Sankar, 1994; Rey et al., 2000; Foneseca et al., 2005; Clemens et al., 1997; Goldwater, 1997; Haubitz et al., 1996; Zuckerman et al., 1997; Heineman et al., 1999; Shapira et al., 2001; Zuckerman & Zuckerman, 2002).
- It is probable that booster doses of vaccine are not required for at least fifteen years in immunocompetent children and adults who have responded to an initial vaccine course (Level of evidence III, Grade B recommendation) ("Are booster immunizations needed," 2000; Jack et al., 1999; Yuen et al., 1999) although in those vaccinated in infancy there is a 5% chronic infection rate after 14 years in high prevalence areas (Whittle et al., 2002). HIV-positive and other immunocompromised patients will still need to be monitored and given boosters when anti-HBs levels fall below 100 IU/L (Level of evidence III, Grade B recommendation) (Rey et al., 2000; Fonseca et al., 2005; "Are booster immunizations needed," 2000).
- Evidence suggests that if vaccine courses are not completed in immunocompetent patients, the outstanding doses can be given four or more years later without the need to restart a three-dose course (Level of evidence III, Grade B recommendation) (Wistrom et al., 1999). One or two doses of vaccine may provide immunity in 40% and over 90% of immunocompetent patients respectively (Wistrom et al., 1999; Marsano et al., 1998).

Table. Vaccination Schedules for Hepatitis B Using Monovalent Vaccine or Combined A+B Vaccine ("Hepatitis B," 1996; Palmovic et al., 1993; Francis et al., 1982; Nothdurft et al., 2002; Saltoglu et al., 2003; Carlsson et al., 1999; Kallinowski et al., 2003; Wright, Campbell, & Tompkins, 2002)

Vaccination Schedule	Advantages	Disadvantages
0, 7, 21 days, 12 months	Rapid immunity Short duration High antibody titres at 12 and 13 months	Little information on HIV or other immunocompromised patients Low antibody titres in the first year (but current evidence suggests that protection is still adequate in the immunocompetent)

Vaccination Schedule	Advantages	Disadvantages
	Potential for better uptake	
0, 1, 2, 12 months	• Shorter time to early immunity than the 0, 1, 6 course • High antibody titres at 12 and 13 months	• Antibody titres lower than the 0, 1, 6 in the first year
0, 1, 6 months	• Higher antibody titres at 7 months than other two regimens, although this may not be clinically important • Long established regimen • Most researched in HIV	• Poor uptake of the 6 month dose in the clinical setting

Hepatitis D (Delta Virus Infection, HDV)

This is an incomplete ribonucleic acid (RNA) virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of intravenous drug users (IVDUs) and their sexual partners but also is seen in female sex workers, and sporadically in other groups (Mele et al., 1988). Suspect hepatitis delta virus (HDV) infection in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis, or if the liver disease in chronic hepatitis B virus is rapidly progressive (McIntyre, 1990; Bianco et al., 2003; Hoofnagle, 1990; Gitlin, 1997). There is a high rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis (McIntyre, 1990; Bianco et al., 2003; Hoofnagle, 1990). Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test (Kotwal, 2000; Gitlin, 1997). Response to anti-viral therapy is poor (Puoti et al., 1998; Lau et al., 1999).

Hepatitis C Virus (HCV) Infection

Diagnosis

Serology

- A screening antibody test such as an enzyme-linked immunoassay (ELISA) or other immunoassy is initially performed and if positive a second test, such as a recombinant immuno-blot assay (RIBA), third generation immunoassay, or reverse transcription--polymerase chain reaction (RT-PCR) for RNA is used to confirm infection (Polish et al., 1999; Thio et al., 2002; el-Dalil et al., 1995; Young et al., 2002; Abel-Hamid et al., 2002; Ross et al., 2002; Mohan et al., 1999). An antibody test may not become positive for three or more months after acute infection but a test for HCV-RNA will be positive after only two weeks. Chronic infection is confirmed if an HCV-RNA assay is positive six months after the first positive test. Patients with low-level viraemia may require HCV-RNA levels testing on two or more occasions to confirm infection. All patients being considered for therapy should have a viral RNA test to

confirm viraemia and genotype assay (see flow chart in original guideline document entitled "Flow chart for hepatitis C testing using an ELISA assay").

Other Tests

- Acute infection, as for hepatitis A
- Chronic infection, as for hepatitis B

Management

General Advice

- Patients should be told not to donate blood, semen, or organs and given advice on other routes of transmission (see below) (Level of evidence III, Grade B recommendation) (Lamden et al., 1998).
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information.
- Acute hepatitis C infection is a notifiable disease.

Further Investigations

As for hepatitis B.

Treatment

- Acute icteric hepatitis: there is some evidence that high dose alpha interferon given during the acute phase will reduce the rate of chronicity to only 10% (Level of evidence IIb, Grade B evidence) (Poynard et al., 2002; Jaekel et al., 2001). Spontaneous resolution of acute hepatitis C is signified by a loss of HCV-RNA within the first month of symptoms. Only those HCV-RNA positive for more than a month need to be treated (Hofer et al., 2003). Otherwise manage as for hepatitis A.
- Chronic infection: Peginterferon alpha with ribavirin will abolish chronic infection in approximately 50% of patients and is the approved therapy of the National Institute for Health and Clinical Excellence (NICE) (Level of evidence Ia, Grade A recommendation) (NICE, 2004). Treatment should be for 24 weeks for patients with genotypes 2 or 3. Other genotypes should be treated for 12 weeks and treatment only continued if there has been a reduction in HCV viral load to 1% of the level at the start of treatment. Patients achieving this 2 $\log_{10}$ reduction should be treated for 48 weeks in total. Patients are more likely to respond if they have less severe liver disease (low fibrosis index on liver biopsy), low serum HCV-RNA levels (<2 million RNA copies/mL), if they are infected with certain HCV sub-types (types 2 and 3), or if they become HCV-RNA negative in the serum within 12 weeks (Level of evidence Ib, Grade A recommendation) (NICE, 2004; Manns et al., 2001; Fried at al., 2002; Hadziyannis et al., 2002; Heathcote et al., 2000).
- HIV-positive patients respond to treatment, although not as well as HIV-negative patients, and should be considered for therapy (Level of evidence IIa, Grade B recommendation) (Nelson et al., 2003; Torriani et al., 2004;

Carrat et al., 2004; Chung et al., 2004). Sustained virological response in those completing therapy is 11 to 29% for genotypes 1/4 and 43–73% for genotypes 2/3 (Level of evidence 1b, Grade A recommendation) (Torriani et al., 2004; Carrat et al., 2004; Chung et al., 2004).

- Patient selection for therapy depends on liver histology, HCV genotype, and viral load (NICE , 2004; Manns et al., 2001; Fried at al., 2002; Hadziyannis et al., 2002; Heathcote et al., 2000; Torriani et al., 2004; Carrat et al., 2004; Chung et al., 2004).
- Given the high rate of fulminant hepatitis in co-infection hepatitis A and C and the worse prognosis of hepatitis B and C co-infection, patients with hepatitis C should be vaccinated against hepatitis A and B (Level of evidence III, Grade B recommendation) (Pramoolsinsap, 2000; Vento et al., 1998; Liaw, 2002).

Pregnancy and Breast Feeding

- There is at present no known way of reducing the risk of vertical transmission. Women should be informed of the potential risk of transmission in pregnancy (see "Transmission" section in original guideline document) (Level of evidence IV, Grade C recommendation) (Dienstag, 1997).
- Breast feeding: there is no firm evidence of additional risk of transmission except, perhaps in women who are symptomatic with a high viral load (Level of evidence III, Grade B recommendation) (Kumar & Shahul, 1998; Conte et al., 2000; Polywka et al., 1999)

Sexual and Other Contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious (Level of evidence IV, Grade C recommendation) (Oxman et al., 1994). The infectious period is from 2 weeks before the onset of jaundice in acute infection. If there was no acute infection, trace back to the likely time of infection (for example, blood transfusion, first needle sharing) although this may be impractical for periods longer than 2 or 3 years. Consider testing children born to infectious women (Level of evidence IV, Grade C recommendation) (Dienstag, 1997). For other non-sexual contacts thought to be at risk, discuss with the CCDC or equivalent.
- There is currently no available vaccine or immunoglobulin preparation that will prevent transmission.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided, but given the very low rate of transmission outside HIV co-infection (see above), monogamous partners may choose not to use them (Level of evidence IV, Grade C recommendation).

Follow-up

- As for hepatitis B (Level of evidence IV, Grade C recommendation)
- Immunity is probably sub-type specific only; there are at least seven sub-types. (Young et al., 2002; Abdel-Hamid et al., 2002; Ross et al., 2002)

Screening and Primary Prevention

- Consider testing for hepatitis C in all intravenous drug users, especially if equipment has been shared, in hemophiliacs or other patients who received blood or blood products pre-1990, and in people sustaining a needle-stick injury if the donor HCV status is positive or unknown (Level of evidence III, Grade B recommendation) (Lamden et al., 1988; Kaldor et al., 1992; Ramsay et al., 1998; Hamid et al., 1999; Sawayama et al., 2000; Bodsworth et al., 1996; "Hepatitis C virus," 1993). Other groups to be considered for testing are sexual partners of HCV positive individuals, men who have sex with men (MSM), all HIV-positive individuals, female sex workers, tattoo recipients, alcoholics, and ex-prisoners (Level of evidence III, Grade B recommendation) (Ward, Day, & Weber, 1999; Lamden et al., 1998; Tedder et al., 1991; Bodsworth et al., 1996; Kao et al., 2000; Guadagnino et al., 1998; Satoglu et al., 1998; Mesquita, Granato, & Castelo, 1997; Balasekaran et al., 1999; Delage et al., 1999). It may take 3 months or more for the anti-HCV test to become positive after exposure (see "Incubation period" in the original guideline document).
- Since 1990 all donated blood in the United Kingdom has been screened for HCV and all blood products rendered incapable of transmitting infection (Evidence level III, Grade B recommendation) (Regan et al., 2000).
- Needle and syringe exchange schemes have led to a fall in parenterally transmitted infections including HCV, hepatitis B virus (HBV), and HIV, although not consistently (Level of evidence III, Grade B recommendation) (Hagan et al., 1999; Goldberg, Cameron, & McMenamin, 1998; van Beek et al., 1998).

Definitions:

The following rating scheme was used for major management recommendations.

Levels of Evidence

Ia

- Evidence obtained from meta-analysis of randomised controlled trials

Ib

- Evidence obtained from at least one randomised controlled trial

IIa

- Evidence obtained from at least one well designed controlled study without randomisation

IIb

- Evidence obtained from at least one other type of well designed quasi-experimental study

III

- Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies

IV

- Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grading of Recommendations

A (Evidence levels Ia, Ib)

- Requires at least one randomised controlled trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation

B (Evidence levels IIa, IIb, III)

- Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation

C (Evidence level IV)

- Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities
- Indicates absence of directly applicable studies of good quality

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is graded and identified for select recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Appropriate diagnosis, management and treatment of patients who have viral hepatitides A, B, or C
- Decreased rates of infection of viral hepatitides A, B, or C
- Decreased morbidity and mortality due to viral hepatitides A, B, or C infection and complications of infection

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The recommendations in this guideline may not be appropriate for use in all clinical situations. Decisions to follow these recommendations must be based on the professional judgement of the clinician and consideration of individual patient circumstances and available resources.
- All possible care has been undertaken to ensure the publication of the correct dosage of medication and route of administration. However, it remains the responsibility of the prescribing physician to ensure the accuracy and appropriateness of the medication they prescribe.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

United Kingdom national guideline on the management of the viral hepatitides A, B & C. London (England): British Association for Sexual Health and HIV (BASHH); 2005. 22 p. [191 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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GUIDELINE DEVELOPER(S)

British Association for Sexual Health and HIV - Medical Specialty Society

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GUIDELINE COMMITTEE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The author is supervising treatment of patients with human immunodeficiency virus and hepatitis B in a clinical trial sponsored by Gilead Pharmaceuticals but is not receiving any personal funding.

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD). 2002 national guideline on the management of the viral hepatitides A, B, and C. London (England): Association for Genitourinary Medicine (AGUM), Medical Society for the Study of Venereal Disease (MSSVD); 2002. Various p.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Association for Sexual Health and HIV Web site.

AVAILABILITY OF COMPANION DOCUMENTS

Audit Criteria are available in the original guideline document.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on December 8, 2000. The information was verified by the guideline developer on January 12, 2001. This summary was updated again on August 5, 2002. This summary was updated on November 27, 2002. This summary was updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisory on COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This NGC summary was updated by ECRI on November 1, 2005. The updated information was verified by the guideline developer on January 19, 2006. This summary was updated by ECRI on April 16, 2007, following the U.S. Food and Drug Administration advisory on Baraclude (entecavir). This summary was updated by ECRI Institute on September 5, 2007, following the revised U.S. Food and Drug Administration advisory on Baraclude (entecavir).

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